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Predictors and outcomes of patients with COVID-19 admitted to intensive care units in Pakistan and the development of nosocomial fungal infections: Findings and implications

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ABSTRACT

Objectives: Patients with COVID-19 admitted to intensive care units (ICUs) typically have many complications and co-morbidities, including secondary bacterial and fungal infections, which increase morbidity and mortality. The first step to address this is to measure the prevalence rates, predictors of fungal infections, and outcomes of patients with COVID-19 admitted to ICUs in Pakistan.
Methods: Retrospective review of medical records of patients admitted with COVID-19 to the ICUs of six tertiary care hospitals in Pakistan between March 2020 and June 2023.
Results: A total of 636 patients were included; 68.9% were aged ≥50 years and 62.6% were male. Diabetes mellitus was the commonest co-morbidity (23.7%). A total of 67.8% of patients had severe COVID-19, with 23% critical cases. Antibiotics and antipyretics (all patients) were the most frequently prescribed medicines, along with corticosteroids (72.5%). A total of 63 nosocomial fungal infections developed in 53 patients, with mechanical ventilation and tracheal intubation being significant predictors of secondary fungal infections among patients with COVID-19. The mortality rate was 4.9%, with secondary fungal infections significantly associated with higher mortality.
Conclusions: Approximately 8% of patients with COVID-19 admitted to the ICUs of tertiary developed secondary fungal infections associated with greater mortality. The key factors associated with secondary fungal infections need to be carefully monitored to reduce future mortality in these patients. We will continue to monitor the situation.

Introduction

COVID-19 had a significant impact worldwide on morbidity, mortality, and costs since its emergence in December, 2019, with low- and middle-income countries (LMICs) having a disproportionately higher burden than high-income countries [1]. This is exacerbated by typically inadequate health care infrastructures, sub-optimal viral infection management, poor infection prevention and control measures, and insufficient diagnostic facilities [1].

Pakistan is an LMIC in South Asia, with a currently a sub-optimal but evolving health infrastructure dealing with infectious diseases. The first positive case of COVID-19 was reported on February 26, 2020 in

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Pakistan [2], with the first wave peaking on June 14, 2020, with successive waves there after [2]. During this time, the Government of Pakistan instigated multiple measures to try and mitigate the spread of infection. These included raising awareness among the general population, instigating social distancing and the wearing of face masks in public places, and introducing quarantine areas, particularly, in airports [3]. In addition, COVID-19 wards were established in almost every hospital to manage COVID-19 cases [3].

Overall, more than 1,581,936 positive cases of COVID-19 with 30,664 deaths were reported in Pakistan up to the end of the sixth wave (December 2023) [4]. Although most of the positive cases of COVID-19 in Pakistan manifested with no or only mild to moderate symptoms, severe cases typically required hospitalization, including admission to intensive care units (ICUs) [5].

Since the emergence of COVID-19, many pharmacologic entities have been used for the potential treatment of hospitalized patients with COVID-19. These include antipyretics, antibiotics, antihistamines, corticosteroids, and anticoagulants, as well as antivirals, lopinavir/ritonavir and remdesivir [6]. However, a number of these medicines failed to demonstrate any significant benefit, limiting their subsequent use [6], with only corticosteroids showing benefit [7]. In addition, there have been concerns with excessive use of antibiotics to treat patients with COVID-19, including among both sectors in Pakistan, adding to antimicrobial resistance despite often limited evidence of bacterial co-infections or secondary infections [8–10].

Patients admitted to the ICUs due to COVID-19 can face many complications, including health care–associated infections [5,11,12]. For example, the risk of ventilator-associated pneumonia increases to 50% among patients with COVID-19 in ICUs [13]. Secondary bacterial or fungal infections are also frequently reported among patients with COVID-19 admitted to ICUs, including patients in Pakistan [9,14]. Secondary fungal infections have also been seen in patients with COVID-19 admitted to ICUs in other LMICs, with reported prevalence rates of 32.8% in Egypt [15] and 5.1% in Turkey [16]. This is important given the increasing concerns with the morbidity, mortality, and associated costs with severe fungal infections [17], alongside increasing rates of antifungal resistance [18]. Consequently, the objectives of this study were to measure the prevalence of secondary fungal infections among patients with COVID-19 admitted to ICUs in Pakistan, as well as key factors and outcomes associated with these patients. Our results should help provide potential guidance on possible ways forward to reduce morbidity and mortality in these patients in future pandemics.

Materials and methods

Study settings, design, and location

A retrospective medical record review study was conducted in May and June 2023 to collect data from all patients with COVID-19 admitted to the ICUs of COVID-19 wards among six public sector tertiary care hospitals in the Province of Punjab from the start of the pandemic to June 2023. Punjab was selected for this study because it is the most populous Province in Pakistan. In addition, there are pertinent background data for this study based on previous studies undertaken in this province since the start of the pandemic [5,9,19].

These six hospitals were purposely selected because all these health facilities served as referral hospitals for all patients from primary and secondary hospitals in Punjab during the COVID-19 pandemic whatever their background. Each of these six hospitals had functional COVID-19 wards with a bed capacity of 40-50 beds per institution, along with ICUs containing 10-15 beds. In addition, each of these health facilities had trained health care workers and diagnostic facilities to provide appropriate care to patients with COVID-19. This is different from likely patients seen in private hospitals.

Study variables

The data collection form was designed to collect the variables of interest based on previous studies conducted by the co-authors [5,9,19]. We have used this methodology before where no specific data collection forms were available [5,9,19].

The following variables were recorded on the data collection form:

- Demographics and disease-related details, which included the patient's age, sex and length of hospital stay (days). The age distribution of patients with COVID-19 was grouped into categories, i.e. 10-30, 31-50, and >50 years, based on previous studies conducted by the co-authors in patients hospitalized with COVID-19 [9].
- The existence of any co-morbidities, including diabetes mellitus, hypertension, cardiac diseases, and respiratory diseases.
- Presenting symptoms, including fever/chills, cough, sore throat, shortness of breath, headache or joint/muscle ache, and nausea/vomiting.
- Laboratory findings, including X-rays; white blood cell counts count; and C-reactive protein (CRP), D-dimer, and serum ferritin levels. The X-ray findings were reviewed by medical doctors and the treating physician was consulted in case of any confusion. Normal ranges of white blood cell counts, C-reactive protein, D-dimer, and serum ferritin were taken from the references mentioned on the testing kits available at these hospitals.
- Whether patients with COVID-19 were on oxygen therapy or not during hospitalization.
- The severity of COVID-19 among admitted patients. The severity of COVID-19 was categorized as asymptomatic, mild, moderate, severe, or critical, as per the guidelines issued by the Ministry of National Health Services, Regulation and Coordination, Government of Pakistan [5]:
    - Asymptomatic: SARS-CoV-2 infection (positive polymerase chain reaction) reported but without any symptoms.
    - Mild: Symptoms due to COVID-19 but without any chest X-ray abnormalities and hemodynamic disturbances. The oxygen saturation levels in these patients were ≥94%.
    - Moderate: Patients having a chest X-ray with infiltrates involving <50% of the total lung fields, with oxygen saturation <94% but >90%, and without severe manifestations of the symptoms.
    - Severe: Those with fever, cough, and shortness of breath, as well as a respiratory rate <30, chest X-ray with infiltrates involving <50% of the total lung fields, severe respiratory distress, and oxygen saturation ≤90% on room air.
    - Critical: Worsening of respiratory symptoms, including presence of acute respiratory distress syndrome, bilateral opacities or lung collapse in chest X-ray or computed tomographic scan, and respiratory or cardiac failure.
- Medications administered during their hospital stay.
- Types of devices administered to patients during their hospitalization, including mechanical ventilation, central venous catheters, and urinary catheters.
- Existence of secondary fungal infection during hospitalization, including the name of fungal species microbiologically and clinically.
- Immediate outcomes, that is, whether a patient was discharged alive and well from a hospital or died in the hospital.

Data collection process

Data were collected by a team of investigators comprising health care workers, including medical doctors, pharmacist, and pharmacy and laboratory technicians. Before commencing data collection, the principal investigator (ZUM) provided 2 days of training to all investigators, including interpretation and recoding of the data on the specific data collection form.

The data collection process was initiated after ethics approval and permission from the administrators/authorities of the participating hospitals. The team of investigators visited the medical records rooms of the COVID-19 wards and accessed all the records of patients, with their medical records available manually in paper form. Clinical staff at the participating hospitals were approached where clarity was needed in terms of accessing patient records/information recorded, including X-ray findings and disease severity.

Inclusion and exclusion criteria

All patients who were admitted into the ICUs of COVID-19 wards of the selected tertiary hospitals since the start of COVID-19 pandemic in the country were included in the study. Those patients with COVID-19 who were not admitted to the ICUs, admitted in other health facilities, or whose medical records were not available or incomplete for any reason upon examination were excluded from the study.

Data analysis

Data were entered in the Microsoft Excel and were imported into the IBM SPSS version 25 for statistical analysis after suitable coding and data cleaning. Demographic and clinical features were described descriptively using number and percentages.

A series of univariate analysis were conducted to determine key factors associated with the development of nosocomial fungal infections with demographic. Variables having $P < 0.25$ were simultaneously entered into the multivariate logistic regression model to assess the predictors of fungal infections in patients with COVID-19 in the ICU (dependent variable = fungal infection (no/yes), model = enter). Furthermore, the predictors of mortality were also determined using logistic regression analysis. Statistical significance was taken as $P < 0.05$.

Results

The data of 636 patients admitted to the ICUs with COVID-19 were included in the analysis, with the patients' demographic and clinical features provided in Table 1. The majority of admitted patients were over the age of 50 years (68.9%), with a preponderance of males (62.6%). Nearly half (49.5%) had no co-morbidity. Among admitted patients with chronic diseases, diabetes and hypertension were the most common.

Most frequently observed symptoms were fever (98.4%), dyspnea (63.7%), cough (49.5%), myalgia (45.1%), and a sore throat (39%). As expected, the majority of the patients had severe COVID-19 (67.8%), with 23% critical cases. 91.8% of patients required oxygenation, with 14.8% requiring invasive mechanical ventilation. Most patients had 15-21 days of stay in the hospital (35.1%).

The most commonly used medication classes were antibiotics (100%), antipyretics (100%), vitamins (75.5%), corticosteroids (72.5%), and antihistamines (69.5%) (Figure 1).

As shown in Table 2, 63 nosocomial fungal infections developed in 53 patients. Of those patients who developed nosocomial fungal infections, 24 had candidiasis, 15 aspergillosis, and 24 mucormycosis. Treatment was typically nystatin/fluconazole; however, this varied depending on the nature of the fungal infection.

The predictors of nosocomial fungal infections in patients with COVID-19 are shown in Table 3. A series of univariate analysis was performed to determine the suitable covariates for the multivariate analysis. As mentioned, covariates having $P < 0.25$ were considered for further analysis. In the multivariate analysis (dependent variable = nosocomial fungal infection; method = enter), being on invasive mechanical ventilation was significantly associated with a greater risk of developing a nosocomial fungal infection (odds ratio = 4.331, 95% confidence interval 1.901-9.866, $P < 0.001$).

Table 1
Demographics and clinical features of the sample.

Variable	N (%)
Age (years)	
≤30	52 (8.2)
31-50	146 (23.0)
>50	438 (68.9)
Sex	
Male	398 (62.6)
Female	238 (37.4)
Residence	
Rural	
Urban	249 (39.2)
Comorbidities	387 (60.8)
Diabetes	151 (23.7)
Hypertension	120 (18.9)
Heart disease	59 (9.3)
Respiratory disorder	30 (4.7)
Others	5 (0.8)
Symptoms at presentation	
Fever	626 (98.4)
Cough	315 (49.5)
Runny nose	72 (11.3)
Sore throat	248 (39.0)
Headache	184 (28.9)
Myalgia	287 (45.1)
Fatigue	127 (20.0)
Dyspnea	405 (63.7)
Nausea and vomiting	122 (19.2)
COVID severity	
Moderate	59 (9.3)
Severe	431 (67.8)
Critical	146 (23.0)
Laboratory findings	
Abnormal X-ray	365 (57.4)
Abnormal white blood cell count	589 (92.6)
Abnormal C-reactive protein	443 (69.7)
Abnormal D-Dimer	370 (58.2)
Abnormal serum ferritin	215 (33.8)
Oxygen therapy	
Yes	592 (91.8)
No	52 (8.2)
Medical devices	
Invasive mechanical ventilation	94 (14.8)
Central venous catheter	26 (4.1)
Urinary catheter	174 (27.4)
Length of stay (days)	
≤7	44 (6.9)
8-14	68 (10.7)
15-21	223 (35.1)
22-29	160 (25.2)
≥30	141 (22.2)

Table 2
Prevalence of fungal infections and associated treatment among patients.

	N (%)	
Fungal infection		
Yes	53 (8.3)	
No	583 (91.7)	
Type of infection (N = 63)	**N**	**Antifungal treatment**
Candida albicans	7	Nystatin/Fluconazole
Candida glabrata	2	Nystatin/Fluconazole
Candida parapsilosis	6	Nystatin/Fluconazole
Candida auris	9	Nystatin/Fluconazole
Aspergillus	15	Voriconazole/itraconazole
Mucormycosis	24	Amphotericin B/posaconazole/itraconazole

Regarding the outcome, the majority of the patients made a complete recovery and were discharged from the hospital (95.1%), whereas 4.9% succumbed to their illness. Being on mechanical ventilation and the presence of nosocomial fungal infections were associated with higher odds of mortality (Table 4).

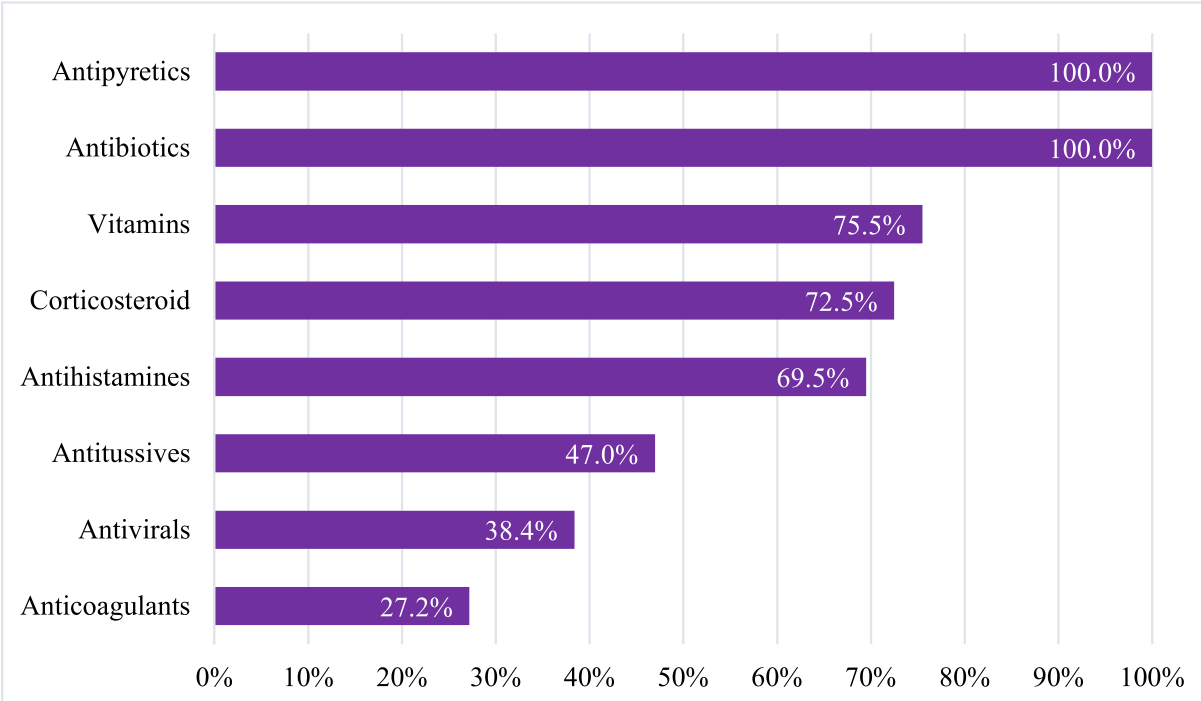

Figure 1. Commonly prescribed medicines among admitted patients.

Table 3
Predictors of fungal superinfection in the sample.

Covariates	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age (years)				
≤30	1.00 (Ref.)	–		
31-50	1.073 (0.279-4.126)	0.918		
>50	1.687 (0.503-5.652)	0.397		
Gender				
Male	1.00 (Ref.)	–		
Female	0.929 (0.517-1.669)	0.805		
Diabetes	1.582 (0.861-2.907)	0.139	0.824 (0.400-1.695)	0.598
Hypertension	1.287 (0.655-2.532)	0.464		
Heart disease	2.534 (1.200-5.353)	0.015	1.922 (0.812-4.552)	0.137
Respiratory disorder	0.777 (0.180-3.357)	0.736		
COVID-19 severity				
Moderate	1.00 (Ref.)	–		
Severe	0.816 (0.178-3.741)	0.794	0.878 (0.178-4.327)	0.873
Critical	10.388 (2.420-44.591)	0.002	3.415 (0.555-21.028)	0.185
Oxygen therapy	2.495 (1.194-5.215)	0.015	1.291 (0.562-2.962)	0.547
Mechanical ventilation	12.805 (6.956-23.571)	< 0.001	4.331 (1.901-9.866)	< 0.001
Central line	4.517 (1.805-11.303)	0.001	2.769 (0.967-7.931)	0.058
Urinary catheter	1.163 (0.629-2.150)	0.630		
Length of stay (days)				
≤ 7	1.00 (Ref.)	–		–
8-14	2.687 (0.290-24.872)	0.384	2.648 (0.263-26.690)	0.409
15-21	0.986 (0.112-8.653)	0.990	1.034 (0.109-9.786)	0.976
22-29	3.174 (0.399-25.284)	0.275	1.561 (0.175-13.961)	0.690
≥ 30	12.624 (1.672-95.267)	0.014	2.869 (0.316-26.082)	0.349
Corticosteroids use	2.258 (1.042-4.892)	0.039	0.582 (216-1.571)	0.285
Antiviral use	3.818 (2.093-6.965)	< 0.001	0.936 (0.409-2.142)	0.876
Anticoagulants	0.859 (0.448-1.649)	0.648		

CI, confidence interval; OR, odds ratio; Ref., reference.

Discussion

The management of severe or critically ill patients with COVID-19 in ICUs possess a great challenge for any health care setting due to the manifestations of a wide range of symptoms, including acute respiratory distress syndrome [20]. Patients with COVID-19 admitted to ICUs are highly vulnerable to developing secondary bacterial or fungal infections, contributing to an unfavorable prognosis, including increased mortality [11,12]. Even in the absence of any other risk factor, severe or critical COVID-19 infections can suppress the immune system of the patients by altering T-cell signaling in a number of ways, rendering patients with COVID-19 at a greater risk of opportunistic infections [21]. In ICUs, the

Table 4
Outcomes of COVID patients who acquired fungal infection.

Covariates	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	P-value
Fungal infection	8.688 (3.946-19.128)	<0.001	2.541 (1.031-6.260)	0.043
Mechanical Ventilation	18.096 (8.021-40.826)	<0.001	13.248 (5.487-31.986)	<0.001

NB: CI, confidence interval; OR, odds ratio.

skin barrier of patients is penetrated repeatedly for testing and for the administration of medicines, further providing direct access to the hosts' interiors and increasing the risk of pathogen colonization.

Others factors responsible for the development of opportunistic bacterial or fungal infections among patients with COVID-19 in the ICUs include unnecessary or excessive antibacterial therapy and corticosteroids, although the latter are seen as lifesaving in patients with severe COVID-19 pneumonitis with hypoxia [7]. Other factors include comorbidities such as diabetes mellitus and hypertension, use of invasive medical devices including central venous catheter, noninvasive mechanical ventilation, and longer stays in hospitalized settings, all of which are factors seen in our study [21]. In our study, we also evaluated the occurrence of fungal superinfections in patients with COVID-19 admitted to the ICU and accessed the predictors and outcomes of these fungal infections. The prevalence of secondary fungal infections in patients with COVID-19 admitted to the ICU was 10.09%, comparable to those from India and Iran where similar proportions of patients with COVID-19 were identified with secondary fungal infections [22,23]. A systematic review and meta-analysis also reported that the overall prevalence of secondary fungal infections in patients with COVID-19 was 12.6% [24]. However, other studies have reported higher rates. This includes 25.2% of patients admitted with COVID-19 to ICUs in Saudi Arabia [14], although rates of only 1.86% were reported in Serbia [25].

Mucormycosis was the most common type (n = 24) of fungal infection in our study population, followed by *Aspergillus* (n = 15), *Candida auris* (n = 9) and *Candida albicans* (n = 7) (Table 2). This is similar to reports from India, Pakistan, and the United States among patients with COVID-19, as well as reports from multi-country studies [26,27]. However, a recent study from Egypt found that the most common fungal infection in patients with COVID-19 was *candidiasis*, followed by *aspergillosis* [15].

Mucormycosis can involve many body organs, including the nose, sinuses, orbit, central nervous system, lung (pulmonary), gastrointestinal tract, skin, jaw bones, and joints. However, the rhino-orbital-cerebral form is the most frequent variety seen in 90% of clinical practice worldwide [28]. The most common factors associated with mucormycosis in patients with COVID-19 were low oxygen (hypoxia), high glucose levels (due to diabetes mellitus as a frequent co-morbidity, corticosteroid-induced hyperglycemia, and new-onset hyperglycemia), an acidic medium (metabolic acidosis, diabetic ketoacidosis), increased iron level (increased serum ferritin), decreased phagocytic activity of white blood cells due to COVID-19–induced immunosuppression, corticosteroids, hematologic and other malignancies, age, and prolonged hospitalization [29].

Mechanical ventilation was the only significant predictor of secondary fungal infection among patients with COVID-19 in our study. Moreover, antibiotic use was universal in our study sample. A previous study conducted in these hospitals also revealed that mechanical ventilation was associated with hospital associated infections among patients with COVID-19 and their impact on patient outcomes, similar to other studies [5]. Negm *et al.* [15] also reported that corticosteroid use among hospitalized COVID-19 was associated with secondary fungal infections. However, we did not observe this in our multivariate analysis, which is encouraging given the documented benefits of prescribing steroids in patients with COVID-19 receiving either invasive mechanical ventilation or oxygen alone [7].

Regarding patient outcomes, our study showed that the mortality rate was high among patients with COVID-19 admitted in the ICU who developed secondary fungal infections, similar to the findings of other studies across countries [15,30]. These all suggest that the existence of secondary fungal infections is associated with a higher mortality rate among hospitalized patients with COVID-19 [15,30]. Fungal infections alone were not an independent risk factor for mortality among patients on mechanical ventilation in our study; however, they were a significant predictor of mortality for the entire population in the study. Consequently, patients who are likely to get secondary fungal infections when in ICUs due to their circumstances need to be carefully managed to try and prevent such occurrences. Similarly, there is a need generally to try and prevent fungal infections developing in patients admitted with COVID-19 in the first place through careful monitoring. We will be performing a follow-up on this in future studies.

We are aware that there are a number of limitations with our study. First, we collected data from only public sector tertiary care hospitals, and no private sector hospitals were included. This was deliberate because we did not want income levels to affect the studied population. Second, the appropriate identification of secondary fungal infections using diagnostic bronchoscopy could not always be performed due to the lack of resources and risk of cross-contamination. Third, we collected data retrospectively through examining medical records manually. Consequently, we are unable to establish causation between different factors and the development of secondary infections among patients with COVID-19. In addition, we did not collect any data on antifungal resistance patterns if this was not included in the patients' medical records. However, these issues are normal when using this methodology. Despite these limitations, we believe our findings will facilitate all key stakeholders regarding potential measures to reduce secondary fungal infections among hospitalized patients, particularly, patients with COVID-19 admitted in ICUs.

Conclusion

In patients hospitalized with COVID-19 admitted to ICUs, cell-mediated immunosuppression, impaired glucose tolerance, widespread use of antibiotics and steroids, mechanical ventilation, and orotracheal intubation add to the chances of opportunistic fungal infections. As a result, morbidity, mortality, and costs increase. *Mucormycosis*, *aspergillosis*, and *candidiasis* were the most common fungal infections reported in our study. Given the high mortality, early detection and subsequent management of these fungal infections are key requirements to improve the outcomes for patients with COVID-19 admitted to ICUs. Updating diagnostic facilities in tertiary hospitals in Pakistan can help with rapidly diagnosing secondary fungal infections to treat patients more effectively. In addition, clinicians should focus on the potential risk factors that increase the chances of fungal infections and their impact. This is especially important given the rise in antifungal resistance across different countries in recent years and its associated consequences. We will be performing a follow-up on this in future studies.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical considerations

Ethical approval for the study was obtained from the Office of Research, Innovation and Commercialization, Lahore College for Women University, Jail Road, Lahore. Moreover, ethical approval of the current study was also obtained from all the relevant institutions. Because patient data were being collected retrospectively from medical records and notes, with no data collected directly from patients, the approval committee exempted written informed consent from the participants. No personal information regarding patients was collected by the investigators, and each patient was given a study number, with all data subsequently kept confidential.

Author contributions

The study concept and design were conceived by ZUM, MS, JCM, BG and RAS with subsequent input from all authors. ZUM, AS, MFM, MS, AN, THM, YHK, JCM, BG and RAS were involved with the acquisition of the data, reviewing data quality, verifying the data with different data sources, performing the statistical analyses, and developing the data visualizations. Funding acquisition: ZUM, BG, JCM, RAS. Preparation of first draft of the manuscript: ZUM, JCM, BG, and RAS. All authors edited and revised it critically for important intellectual content.

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